Rett Syndrome: Connecting Science, Clinical Practice, and the Path Forward

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KEY TAKEAWAYS:

- Rett syndrome (RTT) is a rare, complex neurodevelopmental disorder diagnosed clinically with the support of genetic testing. Timely diagnosis requires a high index of suspicion and increased awareness of subtle regression and delay in development[1]
- RTT arises from disrupted neuronal maturation rather than progressive neurodegeneration, with no loss of neurons, preserving the potential to harness neuroplasticity[1-3]
- Without RTT-specific treatment, improvements in core symptoms are generally limited; however, with appropriate intervention strategies, individuals with RTT have the capacity to experience meaningful gains regardless of age or disease severity[1,4-6]

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Timely diagnosis of Rett syndrome

"We have a role as pediatric neurologists to really evaluate the etiology of one's developmental concerns…There may be signs that suggest the child may need genetic testing."

— Dr Rossi

Rett syndrome is a rare, complex, neurodevelopmental disorder diagnosis clinically based on characteristic patterns of regression and stabilization. Typical RTT is defined by all 4 main criteria—ie, loss of spoken language and purposeful hand use, hand stereotypies, and gait abnormalities—while not meeting any exclusion criteria. Atypical RTT is diagnosed when at least 2 main and 5 supportive criteria are met.[1,7]

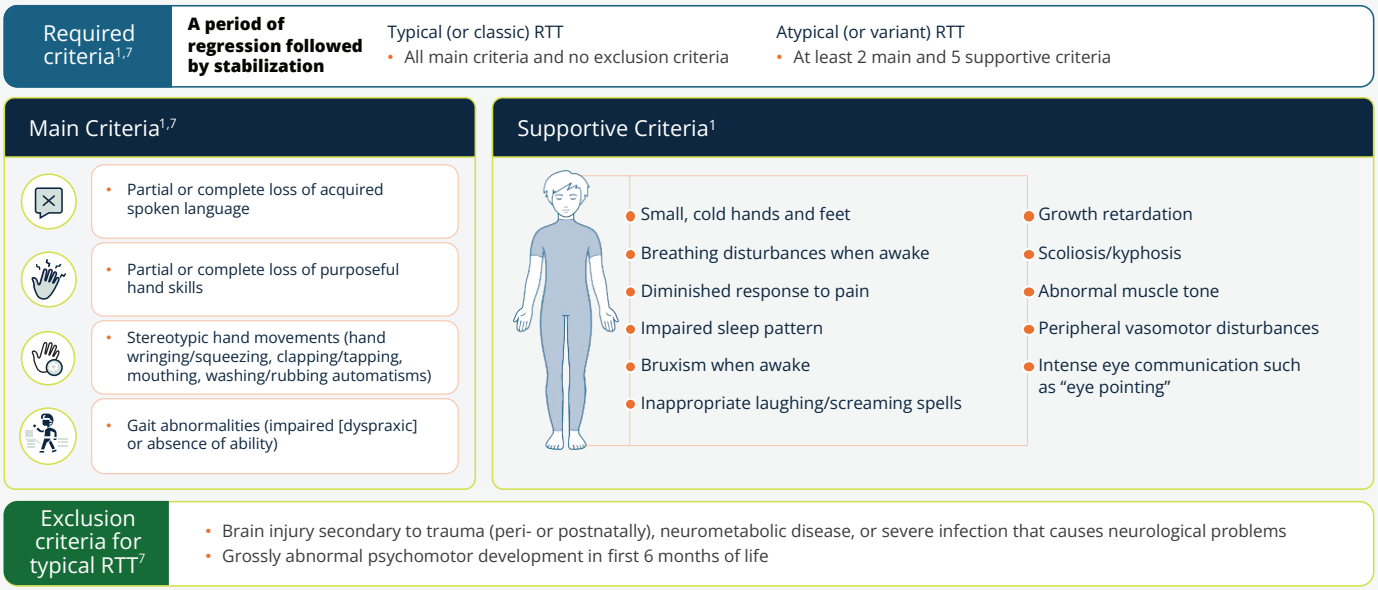

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Figure created based on language from Fu C et al (2020) and Neul JL et al (2010).

Differential diagnoses of RTT due to the possibility of similar presentation or characteristics may include autism spectrum disorder, cerebral palsy, Angelman syndrome, and global developmental delay.[8]

"The loss of hand use and fine motor skills plus stereotypies that impede hand use is very specific to Rett syndrome compared to other neurogenetic conditions."[1]

— Dr Abbott

Timely diagnosis of Rett syndrome

While genetic testing is often used to support a clinical diagnosis, the presence of *MECP2* mutations alone is neither necessary nor sufficient for diagnosis.[1,7] Loss-of-function mutations in the *MECP2* gene were found in ~95% of typical RTT cases and ~73% of atypical RTT cases.[9] However, 3%-5% of patients with clinically defined RTT have no identifiable mutation, and conversely, some individuals with *MECP2* mutations don't exhibit RTT features.[7] Some children with *MECP2* mutations show early signs suggestive of RTT but no loss of skills. These patients, typically under 3 years old, are classified as having "possible" RTT and may be reassessed periodically. If regression occurs, the diagnosis becomes definite RTT; if no regression occurs by age 5, RTT is unlikely.[7]

The median age of RTT diagnosis is 2.7 years for typical RTT and 3.8 years for atypical RTT.[10] Enhanced developmental screening and widespread implementation of *MECP2* testing have contributed to earlier diagnosis of classic RTT over the last 2 decades.[10] However, children who developed and then lost more advanced skills—such as ability to pedal a tricycle, using phrases, or independent walking—and those with unusual, stereotypic hand movements experienced longer duration from regression to diagnosis.[10,11]

"I had one child with mild developmental delays diagnosed with RTT after recovering slowly from a viral illness. It can be easy to brush off a slow recovery as some other reason but, to me, that was a sign. It was a behavioral regression mostly, but looking closer, there was also subtle motor regression and speech regression, from babbling to not making much noise."

— Dr Rossi

A high index of suspicion toward patients between ages 6 months to 3 years and greater awareness of the delay in advanced skills are key to timely diagnosis of RTT. While not diagnostic, potential features like microcephaly should raise concern, and absence of some classic clinical signs should not delay evaluation.[7,10] Timely diagnosis enables genetic counseling, informed family planning, reduced psychosocial stress, and earlier access to intervention services and support programs.[10]

Understanding Rett syndrome

"Even though patients with RTT experience regressions, there is no loss of neurons during this time. The neurons are there but are not fully developed.[1,12] The question becomes, what can we do from a therapeutic perspective?"

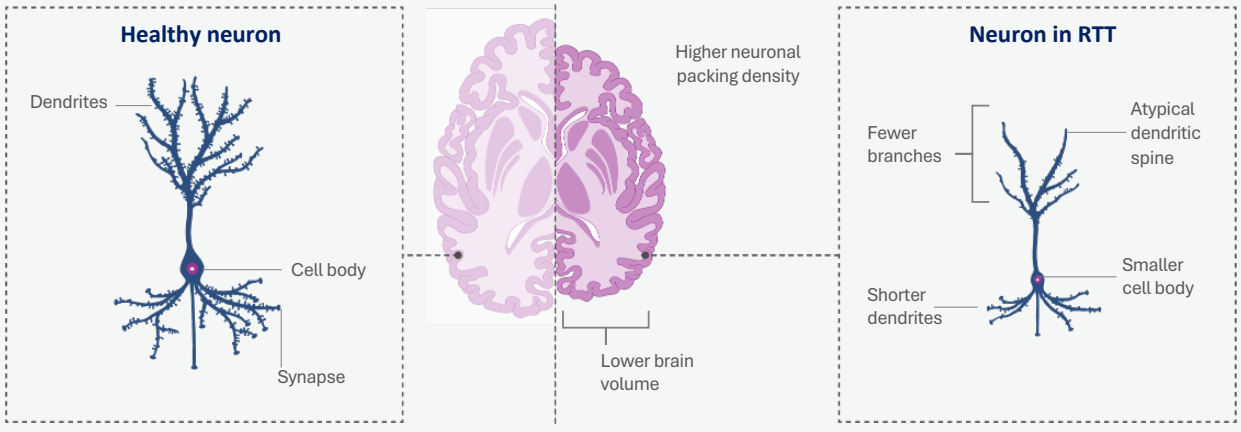
— Dr Abbott

RTT is most often caused by spontaneous mutations in *MECP2* on the X chromosome. In RTT, loss of functional *MECP2* is associated with reduced expression of BDNF and IGF-1, which is thought to contribute to abnormalities in neuronal development, maturation, and synaptic function.[13-15]

BDNF and IGF-1 are *MECP2*-regulated growth factors[14]

- Brain-derived neurotrophic factor (BDNF) supports neuronal differentiation and synaptic plasticity[3,14]
- Insulin-like growth factor 1 (IGF-1) is a key modulator of neuronal growth and maturation[3,16]
- BDNF and IGF-1 share signaling pathways and act together to promote activity-dependent synaptic and cognitive plasticity[3,17]

While neurons in patients with RTT undergo morphological alterations, there is no neuronal loss. Patients with RTT exhibit specific pathological phenotypes, including a reduction in brain volume associated with smaller neurons, decreased dendritic arborization, and overall altered neural circuit structure, suggesting a defect in neuronal maturation. In contrast, a neurodegenerative disorder is characterized by a progressive loss of neurological function and, ultimately, neuronal cell death.[12,18]



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Understanding Rett syndrome

Smaller neurons with underdeveloped dendrites can affect synapses and the excitation-inhibition balance in the brain, resulting in abnormal neuronal firing. This is thought to contribute to the diverse neurological symptoms in RTT, including some cognitive and motor impairments and seizures.[3,12]

As neurons are not progressively lost in neurodevelopmental disorders, such as RTT, the potential to harness neuroplasticity remains.[3,12]

"In Rett syndrome and other neurodevelopmental disorders, we believe that there is progress to be made with targeted therapy."

— Dr Rossi

"I don't put an age limit on the ability to make progress. I have seen patients with Rett syndrome gain new skills in their teens and in their 20s. Therapies still have a lot of value even past the age of 18."

— Dr Abbott

Rethinking potential in Rett syndrome

"With continued care and appropriate therapies, these kids can maintain a very good quality of life, communicating with their families and having meaningful experiences in the community."

— Dr Abbott

Individuals with RTT present clinically with a highly heterogenous set of symptoms.[12] There is increasing evidence that the cognitive ability of patients has been underestimated.[19] Assessments adapted to use eye gaze/eye pointing or eye tracking have revealed a wide range of cognitive abilities in individuals with RTT. Patients with RTT have been known to use various modalities to convey needs/wants, make choices, express discomfort or displeasure, and request attention. Meaning, they also have the potential to have meaningful interactions with others despite variability in expressive and recessive communication abilities.[19-21]

Rethinking potential in Rett syndrome

"Part of my history taking is understanding how do the parents see their child communicating. They are the ones who see that."

— Dr Rossi

"My favorite questions to ask are, 'What does yes look like for your child? What does no look like?' Then it's about sharing that with others to help the child communicate outside the home."

— Dr Abbott

However, without RTT-specific treatment, improvements in core symptoms are generally limited.[4] The Australian Rett Syndrome Study explored the natural history of 298 female patients with RTT over 20 years using a validated, caregiver-rated scale—the Rett Syndrome Behaviour Questionnaire (RSBQ) scale—designed to assess a range of core symptoms including hand movements, breathing, nighttime behaviors, repetitive behaviors, vocalizations, mood, eye gaze, and facial expressions. The study found that in the 5-20 years subgroup, the change in the RSBQ total score was minimal. From a baseline of 43.7 points, there was less than a 1-point reduction at 3 years (-0.30; 95% confidence interval [CI], -1.80 to 1.20) and at a 5-year follow-up (-0.57; 95% CI: -2.29, 1.16).[4,22]

RSBQ is a validated scale that is widely used as an outcome measure in RTT clinical trials. Caregivers rate 45 items as they relate to the child. These items cover a range of common symptoms such as hand movements, breathing, nighttime behaviors, repetitive behaviors, vocalizations, mood, eye gaze, and facial expressions. Each item is rated on a 3-point scale. The scores are added to calculate the RSBQ total score (the maximum possible score is 90). A lower RSBQ score reflects lesser severity in RTT signs and symptoms.[4,22,23]

This highlights the importance of a comprehensive, multifaceted approach to management. Regardless of age or disease severity, individuals with RTT have the capacity to experience symptomatic improvements with appropriate intervention strategies.[1] Preclinical research has shown that brain development continues even after symptom onset and long-term neuronal plasticity could possibly be intact within the cortex in RTT syndrome.[1-3,12] With most individuals with RTT living into adulthood, evolving needs and new science continue to reshape how clinicians optimize care.[1]

Together, these findings and expert perspectives underscore the importance of timely diagnosis and proactive multidisciplinary management in improving outcomes for individuals with RTT. Continued collaboration across specialties and greater awareness of the evolving science in RTT can help unlock each patient's potential and advance the standard of care.[1]

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